

ORIGINAL ARTICLE

# Maternal obesity and its repercussions on melatonin and cortisol in breast milk and human colostrum

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*Manuscript received: may 2022*

*Manuscript accepted: march 2023*

*Version of record online: august 2023*

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**Abstract**

**Introduction:** scientific evidence has highlighted the role of chronobiological disruptions in promoting obesity through mechanisms involving important circadian rhythm hormones: melatonin and cortisol. These hormones are present in human colostrum and serve as crucial maternal and child protection mechanisms against obesity and childhood infections, owing to the intense interaction between mother and child during pregnancy and breastfeeding. Consequently, the melatonin and cortisol hormones present in human colostrum hold promise as potential candidates for yielding clinically applicable results and supporting future intervention strategies aimed at reducing obesity and neonatal infections. However, there is a scarcity of literature on this subject.

**Objective:** the objective of this study is to analyze the impact of maternal obesity on the levels and functions of melatonin and cortisol in colostrum and breast milk.

**Methods:** a systematic review of the scientific literature was conducted following the recommendations outlined in the PRISMA protocol. Original articles published in English were searched in the PubMed, Medline, Lilacs, and Scopus databases. There were no restrictions on the publication year.

**Results:** a total of 37 articles were identified from the searched databases. After removing duplicates and applying the inclusion and exclusion criteria, only five studies were relevant to the topic: two studies addressing melatonin and three studies analyzing cortisol. This review revealed that melatonin levels are elevated in the colostrum of obese women, and for this particular group, it has the potential to restore phagocyte activity and increase lymphocyte proliferation. Studies on cortisol have demonstrated that maternal obesity does not alter the levels of this hormone in breast milk.

**Conclusion:** breastfeeding should be encouraged for all populations, and further original research should be conducted to elucidate the protective mechanisms of colostrum and breast milk.

**Keywords:** colostrum, cortisol, breast milk, melatonin, obesity.

**Suggested citation:** Moreira VAR, Abreu LC, Silva JPC, Pereira GAV, Pereira NNL, Uliana RD, Rodrigues RP, Barbosa MCR, Vieira TS, Morais TC. Maternal Obesity and its repercussions on melatonin and cortisol in breast milk and human colostrum. *J Hum Growth Dev.* 2023; 33(2):277-285. DOI: <http://doi.org/10.36311/jhgd.v33.14580>

## Authors summary

### Why was this study done?

Faced with the increasing prevalence of obesity in women, researchers have investigated possible alterations and effects of melatonin and cortisol in colostrum and human milk resulting from pregnancy affected by maternal obesity. Understanding these effects can guide strategies for addressing obesity and promoting breastfeeding. However, there is a lack of information in the scientific literature regarding cortisol levels in the colostrum of obese women and the mechanisms through which this hormone acts on cellular components derived from colostrum or breast milk in pregnancies impacted by obesity.

### What did the researchers do and find?

The impact of maternal obesity on the levels and actions of melatonin and cortisol in colostrum and breast milk was analyzed based on results published in scientific literature. For this review, scientific articles were extracted from databases such as PubMed, Medline, Lilacs, and Scopus on February 17, 2023, using the keywords: Obesity, Colostrum, Breast Milk, Melatonin, and Cortisol. The conclusions drawn are based on 5 scientific articles that were identified, screened, and deemed eligible for inclusion. Regarding melatonin, it was observed that obese mothers have high levels of this hormone in their colostrum, and specifically for this group, there is a potential for restoring the functional activity of colostrum phagocytes and increasing lymphocyte proliferation. On the other hand, maternal obesity or body mass index does not appear to alter cortisol levels in breast milk.

### What do these findings mean?

This review demonstrates that melatonin is present in higher concentrations in the colostrum of obese women and has the potential to restore the functional activity of colostrum phagocytes to a level similar to that of the eutrophic group, while also increasing the lymphocyte proliferation index. Additionally, maternal obesity does not seem to influence cortisol concentrations in human milk. However, due to the limited number of studies on melatonin and cortisol in human colostrum from pregnant women with obesity, the need for more experimental and observational research on these respective hormones in human milk expressed during the first days after birth is emphasized.

### Highlights

There is an indication that melatonin is elevated in the colostrum of obese women, and specifically for this group, it has the potential to restore the functional activity of colostrum phagocytes and increase the proliferation of lymphocytes.

Melatonin is found in higher concentrations in the colostrum of obese women and has the potential to restore the functional activity of colostrum phagocytes to a level similar to that of the eutrophic group. Additionally, it increases the rate of lymphocyte proliferation. Maternal obesity did not influence cortisol concentrations in human milk.

In a study included in this review, which aimed to determine the influence of maternal and infant biological and sociodemographic factors on the levels of glucocorticoid hormones in human milk, the authors reported that although cortisol levels were similar in the milk of the eutrophic group and overweight and obese women, cortisone levels were significantly higher in normal weight women. Furthermore, there was a strong positive correlation between cortisone and cortisol levels in human milk.

Understanding the changes and effects of melatonin and cortisol in colostrum and human milk caused by obesity can provide knowledge that will serve as guidelines for the development of new biotechnologies mimicking the mechanisms of maternal and child protection. These strategies can be used to address obesity itself and strengthen breastfeeding.

## INTRODUCTION

Obesity is a significant public health issue that affects countries across various income levels, including high, middle, and low-income nations, and its prevalence continues to increase globally. As a chronic and inflammatory disease, it has wide-ranging repercussions on the overall health balance, necessitating interventions by healthcare professionals to mitigate its detrimental effects on the body and improve the population's quality of life.

According to the World Health Organization (2023), obesity has reached epidemic proportions. Globally, more than 1 billion individuals are classified as obese, including 650 million adults, 340 million adolescents, and 39 million children. This widespread issue affects populations in high, middle, and low-income countries alike<sup>1</sup>.

It is well-established that being overweight or obese increases the risk of developing numerous diseases. Some of the conditions associated with excess weight include asthma, musculoskeletal disorders, sleep disorders, type 2 diabetes mellitus, liver and kidney dysfunction, cardiovascular disease, infertility, and various types of cancer. The types of cancer linked to overweight and obesity include breast, endometrial, gallbladder, ovarian, prostate, kidney, liver, and colon cancer<sup>1-4</sup>. Additionally, it has been observed that individuals who are obese are three times more likely to be hospitalized in the case of COVID-19<sup>1</sup>.

It is a complex problem to resolve due to the broad etiology of excess weight that involves genetic,

physiological, cultural, political, socioeconomic<sup>5,6</sup> and environmental factors, such as temperature<sup>7</sup>, rainfall<sup>8</sup> and luminosity<sup>9</sup>.

Obesity is preventable and the key to prevention is to act early, even before the baby is conceived. Adequate nutrition during pregnancy and breastfeeding represent important actions to reduce obesity<sup>1</sup>. Breastfeeding for a duration of 6 months or more, even in the presence of maternal obesity, helps reduce the risk of childhood overweight in the offspring<sup>10</sup>. Therefore, the promotion of breastfeeding should be incorporated into public health initiatives aimed at mitigating the consequences of obesity<sup>1,10</sup>.

Pregnancy affected by obesity or its consequences in the pregnant woman and the offspring leads to alterations in the biochemical, immunological, and hormonal components of colostrum<sup>11-13</sup> and in hormonal levels, including melatonin.

The melatonin hormone is primarily produced by the pineal gland and plays a crucial role in regulating circadian rhythms. It also has physiological functions related to the maintenance of energy homeostasis and is involved in the pathophysiological mechanisms associated with the development and persistence of obesity and metabolic syndrome. Furthermore, melatonin can influence the secretion of adipokines, which are signaling molecules produced by adipose tissue<sup>14-17</sup>.

In addition, colostrum contains an active component of the hormone melatonin. When newborns receive colostrum through breastfeeding, this hormone plays a significant role in synchronizing the biological rhythms between the mother and child. Moreover, melatonin enhances the activity of colostrum phagocytes, thereby bolstering its ability to protect the newborn against pathogens that can cause infections<sup>18-20</sup>.

In the colostrum of obese women, melatonin is found in higher concentrations compared to colostrum from eutrophic women. This increase in melatonin levels has a direct impact on the infant by enhancing the protective activity of phagocytes. This effect is recognized as a potential maternal-infant protection mechanism against obesity<sup>13</sup>. Therefore, maternal melatonin appears to contribute to the development of the offspring's circadian rhythm and provides protective effects against various human conditions, including obesity and metabolic dysregulation<sup>21</sup>.

Melatonin, therefore, is an important hormone present in colostrum. However, it exhibits fluctuations throughout the day in accordance with the circadian rhythm (light/dark cycle) and is influenced by abiotic factors. It is worth noting that this abiotic influence is not limited to melatonin alone. There is metabolic and physiological evidence indicating that other hormones are also closely associated with sleep and circadian rhythms, including cortisol<sup>22</sup>.

Cortisol is the primary circulating glucocorticoid hormone, produced by the hypothalamic-pituitary-adrenal axis, which is one of the main neuroendocrine systems associated with the stress response. In its chronic form, when combined with positive energy balance (positive feedback), cortisol contributes to an increased risk of obesity<sup>23</sup>.

Elevated cortisol levels are associated with obesity<sup>24,25</sup>; however, obese individuals may also have normal levels of this hormone<sup>26,27</sup>.

For the child, cortisol is essential for the development of biological rhythms. After birth, during lactation, cortisol can be transferred to the infant via breastfeeding, providing synchronization between day and night periods<sup>28</sup>.

Cortisol is also involved in inflammatory processes in colostrum cells and contributes significantly to the immune response<sup>29</sup>. Thus, the passive transfer of cortisol helps in immunological protection via breastfeeding in the presence of microorganism, through its ability to modulate the functional activity of colostrum phagocytes<sup>30</sup>.

It is possible that melatonin and cortisol present in colostrum and breast milk represent a mother-infant protection mechanism against both the development of obesity and infections in infants. Therefore, understanding the changes and effects of melatonin and cortisol in colostrum and human milk during pregnancy, influenced by obesity, can provide valuable knowledge for developing new biotechnologies that mimic the protective mechanisms between mother and infant. These findings can also be used as strategies for addressing obesity itself and strengthening breastfeeding practices.

The objective of this study is to analyze the impact of maternal obesity on the levels and functions of melatonin and cortisol in colostrum and breast milk.

## METHODS

This is a systematized review type study, based on the protocol framework of the "Preferred Reporting Items for Systematic Reviews and Meta Analyses" (PRISMA)<sup>31</sup>, but it is not characterized as a systematic review because it does not exhaust all indexing databases of journals. when selecting articles.

The PICO strategy (Patient, Intervention, Comparison and "Outcomes" - outcome) was used, and the initials of the pure acronym were defined as follows:

- P: obese women, I: measurements of hormone levels or the action of the hormones cortisol and melatonin in colostrum or breast milk, C: colostrum or breast milk of eutrophic women and O: relation of maternal obesity to levels of cortisol or melatonin or under the action of these hormones on cell components of colostrum from obese women.

Therefore, this study included original scientific articles that were available in full and published in English up until January 31, 2023. These articles were selected based on their relevance to the proposed theme, while literature review articles and duplicates found in the databases or in different languages were excluded from the analysis.

A systematic literature search was conducted in online databases, including PubMed, Medline, Lilacs, and Scopus, on February 17, 2023. The search utilized the following descriptors and Boolean operators: "Obesity AND Cortisol AND Colostrum," "Obesity AND Cortisol AND Breast Milk," "Obesity AND Melatonin AND Colostrum," and "Obesity AND Melatonin AND Breast Milk."

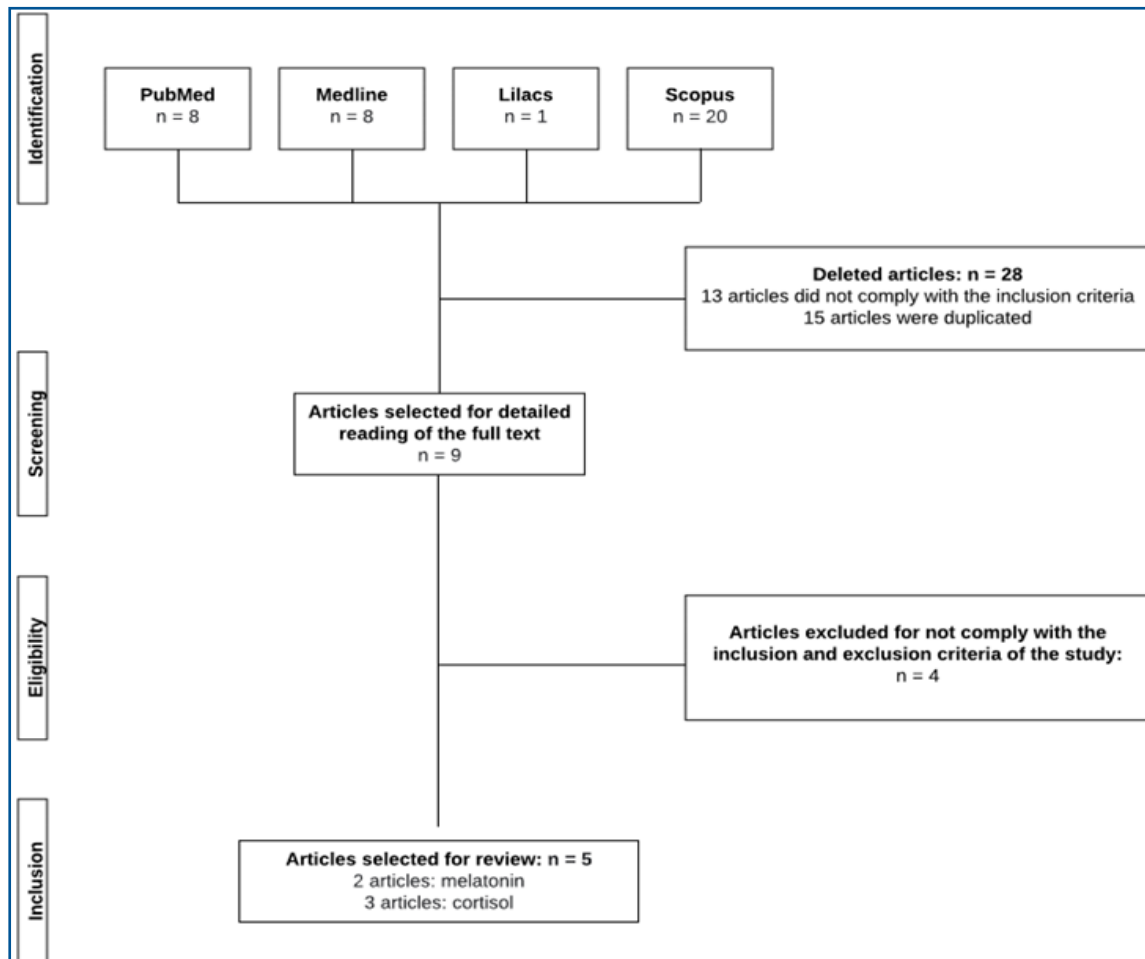
Initially, duplicate articles were identified and excluded using the Zotero program. Following this step, a screening process was performed by reviewing the titles of the articles. Any papers that were deemed unrelated to the topic were excluded. Subsequently, the abstracts of the selected articles were reviewed, and a detailed reading of the full articles was conducted. Articles that did not meet the predetermined inclusion and exclusion criteria were excluded from this review (figure 1).

## RESULTS

37 articles were identified in the PubMed, Medline, Lilacs, and Scopus databases. Among these, 15 articles were excluded as duplicates. After applying the inclusion and exclusion criteria, a total of 5 articles were included in this review. Two articles focused on melatonin, and three studies analyzed cortisol, as shown in Figure 1.

The included articles are described in Table 1. One study investigated melatonin levels in the colostrum of obese women, while two studies examined the effects of melatonin on colostrum cells in obese women.

Regarding cortisol, three studies reported that cortisol levels did not differ in the colostrum of obese women. However, no studies evaluated the effects of cortisol on the cellular components of colostrum or breast milk in the context of maternal obesity (Table 1).



**Figure 1:** Selection flowchart of studies included in the scientific literature review.

**Table 1:** Studies included in the review, distributed according to author and date, objective, type of study, sample used and outcomes.

Author / Data	Desfecho
Pereira <i>et al.</i> , (2023) <sup>32</sup>	<p>Cross-sectional study with laboratory analyses of 52 colostrum samples (26 from obese and 26 from eutrophic mothers), aiming to analyze the repercussions of maternal obesity on the proliferation of human colostrum lymphocytes and the intracellular mechanisms of lymphocyte modulation in the presence of adiponectin, leptin, and melatonin. Melatonin restored lymphocyte proliferation to a level similar to the eutrophic group, accompanied by a reduction in intracellular calcium levels and apoptosis.</p> <p>Lymphocyte proliferation in colostrum was elevated in the overweight group following stimulation with adiponectin, leptin, and melatonin. The eutrophic group exhibited anti-inflammatory action, limited proliferative activity, decreased intracellular calcium levels, and a lower apoptosis rate. Findings strengthen the hypothesis that breastfeeding benefits both maternal and child health by reducing body weight, controlling the inflammatory process, and decreasing childhood infections.</p> <p>The study indicated that the hormones adiponectin, leptin, and melatonin altered the proliferative activity of colostrum lymphocytes in different ways, depending on pre-gestational BMI, suggesting that the modulation of human colostrum lymphocytes is influenced by controlling hormone concentrations and potential differences in receptor expression within these cells.</p>

**Continuation - Table 1:** Studies included in the review, distributed according to author and date, objective, type of study, sample used and outcomes.

Author / Data	Desfecho
Morais <i>et al.</i> , 2019 <sup>13</sup>	<p>Cross-sectional study with laboratory analyses of colostrum from 50 obese and 50 eutrophic women, aiming to analyze the effects of melatonin on mononuclear phagocytes in the colostrum of women with pre-gestational obesity. Colostrum cells from obese individuals exhibited a lower phagocytosis index in mononuclear colostrum cells, but melatonin had the potential to restore the functional activity of these phagocytes to levels similar to those in eutrophic colostrum.</p> <p>Colostrum from the obese group presented higher concentrations of melatonin, mononuclear phagocytes with a lower phagocytosis rate and release of reactive oxygen species, and an increase in intracellular calcium release. Melatonin treatments restored the phagocytosis rate, reduced intracellular calcium release, and decreased the apoptosis index. Melatonin may prevent cellular damage in colostrum cells of obese women through its antioxidant action, potentially representing a mechanism of maternal protection against childhood obesity.</p> <p>The first study to describe melatonin concentrations in colostrum among women with pre-gestational obesity.</p>
Vass <i>et al.</i> , 2020 <sup>33</sup>	<p>Cross-sectional study involving laboratory analyses of 57 samples of breast milk (26 from donors with preterm babies and 31 with term babies), with the aim of investigating potential differences in concentrations of insulin, leptin, cortisol, testosterone, and progesterone between the milk of postpartum women who had preterm and term infants. The study also examines whether pasteurization affects the levels of these hormones. The level of cortisol was not influenced by the maternal body mass index.</p> <p>The hormonal composition of breast milk is affected by Holder pasteurization and maternal obesity. Pasteurized donated milk, when compared to unpasteurized milk, significantly reduces leptin intake and increases cortisol intake.</p> <p>The study highlighted significant differences in the provision of leptin and cortisol to premature infants based on milk origin, with implications for breast milk processing and feeding guidelines.</p>
Lindberg <i>et al.</i> , 2021 <sup>34</sup>	<p>Cohort study involving 340 breast milk donors (32 of whom were obese prior to pregnancy), with the aim of identifying factors associated with cortisol levels in human milk at 2 months postpartum. Maternal obesity did not prove to be a determining factor in significant alterations to cortisol levels in breast milk.</p> <p>Parity and time of year may be important factors to control for when examining cortisol in human milk. Stronger associations were found with maternal and sample characteristics rather than socio-economic and psychosocial distress, which may be attributed to the study being conducted within a low-risk population.</p> <p>The study identified a robust association between the time of year and cortisol levels in human milk, with higher cortisol levels observed in samples collected during the summer.</p>
Pundir <i>et al.</i> , 2019 <sup>35</sup>	<p>Cohort study involving 650 breast milk donors (186 of whom were overweight or obese), with the objective of determining the influence of maternal and infant biological and sociodemographic factors on the levels of glucocorticoid hormones in human milk. Cortisol levels in milk were similar across the groups. Cortisone levels were significantly higher in mothers with normal weight.</p> <p>Concentrations of glucocorticoid hormones are influenced by weight, premature birth, and maternal educational status, suggesting the potential role of maternal biological and social influences in the hormonal composition of milk. Feeding patterns did not influence milk glucocorticoids. Additional analyses are required to fully explore the relationship with maternal stress measures, including maternal glucocorticoid status.</p> <p>This study is the first to investigate the impact of maternal body composition parameters on the glucocorticoid profile of milk and is also pioneering in demonstrating the effect of maternal social and psychological factors on cortisol and cortisone levels in milk.</p>



## DISCUSSION

The literature review yielded results indicating that melatonin levels are elevated in the colostrum of obese women. This increase in melatonin has the potential to restore the functional activity of colostrum phagocytes and enhance lymphocyte proliferation, particularly in this group. However, regarding cortisol, it has been observed that body mass index or maternal obesity do not affect the levels of this hormone in breast milk. There is a dearth of information in the scientific literature regarding cortisol levels in the colostrum of obese women and the mechanisms by which this hormone acts on the cellular components derived from colostrum or breast milk in women with pregnancies affected by obesity.

### Melatonin and maternal obesity

Data on maternal obesity and melatonin in colostrum or human milk are limited in the scientific literature. Only one study from Brazil described melatonin levels in the colostrum of obese women, showing higher levels in the obese group compared to the eutrophic group during daytime collection<sup>13</sup>.

It is important to note that melatonin levels in colostrum may differ from those in blood, as other studies have reported reduced serum melatonin levels in the presence of obesity<sup>16,36,37</sup>. Additionally, studies have shown that restoring melatonin levels can have beneficial effects on lipid profiles, hepatic lipid accumulation, and obesity<sup>38-43</sup>.

The higher melatonin levels observed in colostrum of obese women may represent a beneficial mechanism for promoting protective effects against obesity in infants. However, further studies are needed to explore this topic, as the current research has limitations. The analyzed sample was specific to a particular region, and only daytime colostrum samples were considered, without considering possible circadian disruptions associated with obesity.

Melatonin has also shown an important immunomodulatory role for colostrum mononuclear cells, which are crucial for infant protection against infections and immune response, including phagocytes<sup>13</sup> and lymphocytes<sup>32</sup>. It is known that in the colostrum of obese women, mononuclear phagocytes may exhibit reduced functional activity<sup>13</sup>, and levels of T lymphocytes, CD4+ T lymphocytes, and the proliferation index of total lymphocytes are also diminished<sup>32</sup>.

It is essential to emphasize that the alterations observed in cells do not necessarily imply a decrease in the protective potential of colostrum from obese women. In its natural state, these cells are immersed in an environment containing numerous modulating bioactives, including melatonin<sup>13</sup>. Melatonin in colostrum mononuclear phagocytes from obese women has the potential to restore cell activity to a level similar to that seen in colostrum from eutrophic women<sup>13</sup>. In lymphocytes, melatonin, as well as important adipokines such as leptin and adiponectin, modulate the behavior of colostrum lymphocytes, increasing their proliferation rate and affecting intracellular calcium levels and apoptosis rates<sup>32</sup>.

Understanding the variations in melatonin levels and its actions in human colostrum is crucial for comprehending

the biological mechanisms underlying colostrum's protective effects against the consequences of pregnancy impacted by maternal obesity, ultimately benefiting the infant. This knowledge, which holds potential for clinical application, highlights melatonin as a promising target for interventions aimed at controlling body weight and metabolic diseases associated with obesity.

### Cortisol and maternal obesity

The results of the studies included in this review that analyzed cortisol levels indicated that maternal excess weight was not a determining factor for altering cortisol levels in breast milk<sup>33-35</sup>. However, in blood studies, some indicate high cortisol levels in obese individuals<sup>24,25</sup>, while others describe normal levels<sup>26,27</sup>.

The limited number of studies on the subject contributes to the differences found in each study. Additionally, studies use different assessment methods for cortisol. Isolating serum cortisol levels as a marker is inadequate as it does not represent the actual hormone level available to the cells, nor does it consider its physiological fluctuations, including circadian variations and stress response variations (acute or chronic)<sup>44</sup>.

In one of the included studies, which aimed to determine the influence of maternal and infant factors on glucocorticoid hormone levels in human milk, the authors reported that although cortisol levels were similar in the milk of eutrophic, overweight, and obese women, cortisone levels were significantly higher in normal-weight women. Furthermore, there was a strong positive correlation between cortisone and cortisol levels in human milk<sup>35</sup>.

It is important to note that cortisol is converted to cortisone by enzymes such as the 11 $\beta$ -HSD2 enzyme, which transforms active cortisol into inactive cortisone. These enzymes are potential targets for the treatment of obesity and metabolic syndrome<sup>27,45,46</sup>.

Cortisol can be absorbed from the gastrointestinal tract and affect organ development as well as postnatal adaptation through circulation. It plays an important role in child development<sup>33</sup>.

Exposure to cortisol in breast milk has been associated with a lower absolute body mass index percentile at 2 years of age and may protect female infants against rapid increases in body mass index, suggesting that early exposure to the hormone may provide protection against later obesity and indicate taller and thinner phenotypes<sup>47</sup>. This highlights the importance of cortisol for infant development.

Another relevant finding in the literature is that cortisol concentrations may not change as a result of milk pasteurization<sup>33</sup>, but premature births contribute to elevated cortisol levels<sup>33,34</sup>. Other important factors that influence cortisol levels include the time of day and the stages of milk maturation (colostrum, transitional milk, or mature milk)<sup>28</sup>.

However, it is important to acknowledge the limitations of the studies included in this review, as they do not consider the influence of maternal obesity and cortisol on the different stages of milk maturation and chronobiology. Nevertheless, they provide relevant results that help fill gaps in the scientific literature.

## Study limitation

This study has a limitation in terms of the small number of included studies (n=5). All the studies included in the review provided samples that were representative of specific regional populations from different locations. However, they did not take into account the influence of chronobiology, such as the time of day when the milk collection was performed, or the different stages of milk maturation. This limitation makes it difficult to generalize the data. Nonetheless, despite this limitation, the topic addressed in the study is current, has potential for clinical application, and is highly relevant to the scientific literature.

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## CONCLUSION

Melatonin is present in higher concentrations in the colostrum of obese women and has the potential to restore the functional activity of colostrum phagocytes to a level similar to that of the eutrophic group. It also increases the rate of lymphocyte proliferation.

Maternal obesity does not have an influence on cortisol concentrations in human milk.

## Funding

This study received funding from the State of São Paulo Research Foundation (FAPESP), process number 2019/25112-2.

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## Resumo

**Introdução:** evidências científicas enfatizam que disrupções cronobiológicas podem promover a obesidade por mecanismos envolvendo ação de importantes hormônios marcadores do ritmo circadiano: a melatonina e cortisol. Estes hormônios estão presentes no colostro humano e representam importante mecanismo de proteção materno infantil frente à obesidade e infecções infantis, devido à intensa interação entre mãe e filho durante a gravidez e amamentação. Assim, os hormônios melatonina e cortisol presentes no colostro humano representam promissores candidatos para fornecer resultados com capacidade de aplicação clínica e de embasamento de futuras estratégias de intervenção com enfoque na redução da obesidade e de infecções neonatais. Entretanto, são escassos os estudos na literatura sobre o tema.

**Objetivo:** analisar as repercussões da obesidade materna sobre os níveis e as ações da melatonina e do cortisol no colostro e leite materno.

**Método:** foi realizada uma revisão sistematizada da literatura científica seguindo as recomendações do protocolo Prisma. Foram pesquisados artigos originais, publicados em inglês, nas bases de dados PubMed, Medline, Lilacs e Scopus. Não houve restrição quanto ao ano de publicação.

**Resultados:** foram identificados 37 artigos nas bases de dados pesquisados, 15 artigos foram excluídos por estarem duplicados, após aplicação do critério de inclusão e exclusão apenas 5 estudos tiveram relação ao tema, sendo 2 estudos abordando sobre melatonina e 3 pesquisas que analisaram o cortisol. Esta revisão mostrou que a melatonina está elevada em colostro de obesas e para este grupo ela possui potencial de restaurar atividade de fagócitos e de elevar a proliferação de linfócitos. Os estudos sobre o cortisol ilustraram que os níveis deste hormônio no leite materno não foram alterados pela obesidade materna.

**Conclusão:** o aleitamento materno deve ser encorajado para todos os públicos, assim como mais pesquisas originais devem ser desenvolvidas para descrever os mecanismos protetores do colostro e leite materno.

**Palavras-chave:** colostro, cortisol, leite materno, melatonina, obesidade.

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